Brain dopamine and obesity

Gene-Jack Wang, Nora D Volkow, Jean Logan, Naomi R Pappas, Christopher T Wong, Wei Zhu, Noelwah Netusil, Joanna S Fowler

Summary

Background The cerebral mechanisms underlying the behaviours that lead to pathological overeating and obesity are poorly understood. Dopamine, a neurotransmitter that modulates rewarding properties of food, is likely to be involved. To test the hypothesis that obese individuals have abnormalities in brain dopamine activity we measured the availability of dopamine D2 receptors in brain.

Methods Brain dopamine D2 receptor availability was measured with positron emission tomography (PET) and [C-11]raclopride (a radioligand for the dopamine D2 receptor). Bmax/Kd (ratio of the distribution volumes in striatum to that in cerebellum minus 1) was used as a measure of dopamine D2 receptor availability. Brain glucose metabolism was also assessed with 2-deoxy-2[18F]fluoro-D-glucose (FDG).

Findings Striatal dopamine D2 receptor availability was significantly lower in the ten obese individuals (2.47 [SD 0.36]) than in controls (2.99 [0.41]; p = 0.0075). In the obese individuals body mass index (BMI) correlated negatively with the measures of D2 receptors (r = 0.84; p = 0.002); the individuals with the lowest D2 values had the largest BMI. By contrast, neither whole brain nor striatal metabolism differed between obese individuals and controls, indicating that striatal reductions in D2 receptors were not due to a systematic reduction in radiotracer delivery.

Interpretation The availability of dopamine D2 receptor was decreased in obese individuals in proportion to their BMI. Dopamine modulates motivation and reward circuits and hence dopamine deficiency in obese individuals may perpetuate pathological eating as a means to compensate for decreased activation of these circuits. Strategies aimed at improving dopamine function may be beneficial in the treatment of obese individuals.

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PET Imaging
PET scans were done with a CTI-931 (Computer Technologies, Incorporated, Knoxville, USA) tomograph (resolution 6 × 6 × 6.5 mm full width half maximum (FWHM), 15 slices). Individuals were scanned with [C-11]raclopride and eight of ten individuals were also scanned with FDG. Procedures for positioning of individuals, scanning protocol, and arterial blood sampling were described previously.15,16 Briefly, for [C-11]raclopride, dynamic scans were started immediately after intravenous injection of 4–10 mCi (specific activity ≥0.25 Ci/μmol at time of injection) for a total of 60 min. For FDG, a 20 min emission scan was obtained beginning 35 min after injection of 4–5 mCi of FDG. Arterial blood samples were obtained and used to measure plasma radioactivity and plasma glucose concentration. Metabolic images were computed as described previously.16

Data
Regions of interest in striatum and cerebellum were drawn directly on an averaged emission image (summation of images obtained between 10 min and 60 min for [C-11]raclopride). Regions of interest for striatum were obtained bilaterally from the planes where they were best identified (two slices). Right and left cerebellar (two slices) regions were obtained in the two planes 1.0 cm and 1.7 cm above the canthomeatal line. These regions were then projected into the dynamic images to generate time activity curves for striatum and cerebellum. We calculated average values for the striatal and cerebellar regions from the different slices where the regions were obtained. The time activity curves for tissue concentration along with the time activity curves for unchanged tracer in plasma were used to calculate the distribution volume (mL/gm) and the blood-to-tissue transport constant (K1) in striatum and cerebellum by means of a graphic analyses technique for reversible systems (Logan Plots).17 The measure Bmax/Kd, obtained as the ratio of the distribution volume in striatum to that in cerebellum minus 1, was used to quantify the dopamine D2 receptor availability, that is the number of receptors that are free to bind to the radiotracer. These measurements are insensitive to changes in body weight.19

Brain metabolic images of obese individuals and controls were analysed with regions of interest analysis method. Briefly, regions were selected with a template,16 of 115 non-overlapping regions which were grouped into 12 composite cortical (frontal, parietal, temporal, and occipital cortices, bilaterally), subcortical (striatum bilaterally, thalamus), and cerebellar regions. Measurement of global brain metabolism was obtained by averaging the values from the pixels located in the brain-tissue component of the brain images as previously described.14

Statistical analysis
Differences in the measures of dopamine D2 receptors (Bmax/Kd) in striatum and of metabolism in the 12 composite brain regions between obese individuals and controls were tested by means of the independent sample t test (two-tailed). To correct for multiple comparisons in the metabolic measures incurred by analysing 12 brain regions we set the level of significance at p ≤ 0.01. A repeated measures ANCOVA (analysis of variance and covariance) with repeated measures on the 12 brain regions was also fitted to further examine the effect of sex and BMI on regional metabolism. The link between the dopamine D2 receptor measures and the BMI and other possible covariates was explored with the regression methods.

### Table 1: Average K1 distribution volume (mL/gm), and Bmax/Kd of [C-11]raclopride of obese individuals and controls

<table>
<thead>
<tr>
<th>Parameters/regions</th>
<th>Controls</th>
<th>Obese individuals</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>K1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cerebellum</td>
<td>0.07 (0.01)</td>
<td>0.06 (0.02)</td>
<td>-0.01-0.03</td>
</tr>
<tr>
<td>Striatum</td>
<td>0.12 (0.02)</td>
<td>0.11 (0.02)</td>
<td>-0.01-0.03</td>
</tr>
<tr>
<td>Distribution volume</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cerebellum</td>
<td>0.49 (0.07)</td>
<td>0.48 (0.11)</td>
<td>-0.08-0.10</td>
</tr>
<tr>
<td>Striatum</td>
<td>1.98 (0.37)</td>
<td>1.66 (0.35)</td>
<td>-0.02-0.66</td>
</tr>
<tr>
<td>Bmax/Kd striatum</td>
<td>2.99 (0.41)</td>
<td>2.47 (0.38)*</td>
<td>0.16-0.88</td>
</tr>
</tbody>
</table>

Data are mean (SD). K1=transfer constant of radiotracer from plasma to tissue. Bmax/Kd=ratio of distribution volume in striatum to cerebellum minus 1. *Controls vs obese individuals=p<0.0075.

### Results
Ten severely obese individuals (5 women and five men; mean age 38.9 [SD 7.3] years; age range 26–54 years; BMI range 42–60, mean 51.2 [SD 4.8] kg/m2; body weight 125–177 kg) were selected. The controls were three women and seven men (age range 25–45 years; mean 37.5 [SD 5.9] years; BMI range 21–28, mean 24.7 [SD 2.6] kg/m2; body weight 55–90 kg). The two groups had similar education (obese 14.5 [SD 2.3] years, controls 15 [2.8] years), social, and economic background. The BMI of obese individuals was significantly higher than that of controls (p<0.0001). The estimates of K1 (transfer constant of radiotracer from plasma to tissue) and of the distribution volume of [C-11]raclopride in striatum and in cerebellum of controls did not differ from that of obese individuals (table 1). However, obese individuals had significantly lower measures of striatal dopamine D2 receptor availability (Bmax/Kd: 2.47 [SD 0.36]) than controls (2.99 [0.41]; difference 0.52 [0.17], p<0.0075; figure 1).

The measure of striatal dopamine D2 receptor availability (Bmax/Kd) had a normal distribution. With this measure as the dependent variable, an intensive model fitting (both linear and non-linear) effort showed that the best regression models differ between the obese group and the controls. For the obese individuals, the best model was the simple linear regression model with BMI as the independent variable: Bmax/Kd = -0.0075 + 0.0075 BMI; r2 = 0.41; p<0.001; figure 1).

### Figure 1: Group average images of [C-11]raclopride (distribution volume image) and FDG (metabolic image)

PET for obese individuals and controls at the level of the basal ganglia.

The images are scaled with respect to the maximum value obtained from the controls and presented by means of the rainbow scale. For [C-11]raclopride, red represents the highest value (2.0) and dark violet represents the lowest value (0 ml/Gm). For FDG, highest value is 60 μmol and lowest value is 0 μmol/100 g/min.
the sole regressor (two-sided p value=0·002; figure 2). The striatal dopamine D2 receptor availability had a negative linear link with BMI. The coefficient of determination, which is the square of the usual Pearson product-moment correlation coefficient (r2=0·71), was 0·71. For the controls Bmax/Kd was negatively correlated with BMI; however, this link was not significant. In the controls, age was the best predictor of Bmax/Kd (two-sided p value=0·005); the correlation coefficient was r=−0·80, and the coefficient of determination was 0·64. Neither sex or brain metabolism was significantly related to Bmax/Kd. Because age was not significantly associated with Bmax/Kd for the obese individuals and BMI was not significantly associated with Bmax/Kd for the controls, it was not appropriate to model both groups together.

Our analyses also indicate that the whole brain glucose metabolism (100 g per min) did not differ between obese individuals (37·3 [SD 3·5]) and controls (34·8 [4·1] mmol/100 gm/min; p=0·2; figure 1). Regional brain metabolism was also not significantly different between these two groups (table 2). The repeated measures ANCOVA showed that neither sex nor BMI was related to metabolism.

**Discussion**

We have shown that there is a lower dopamine D2 receptor availability in the striatum of obese individuals than in normal individuals. Moreover, in the obese individuals the D2 receptor measures were negatively correlated with their BMI. The results lead to an association between low D2 receptor amounts in obese individuals or a more-severe eating disorder and higher BMI. Low levels of dopamine D2 receptors have also been reported in individuals addicted to various types of drugs including cocaine,10 alcohol,14 and opiates.20 This would suggest that a reduction in D2 receptors is associated with addictive behaviour irrespective of whether it is due to food, as in this study, or to addictive drugs as seen in substance abusers. Eating is a highly reinforcing behaviour that not only provides nutrients needed for survival, but that also induce feelings of gratification and pleasure.23 Feeding increases extracellular dopamine concentration in the nucleus acumbens,24 which is an effect believed to contribute to the reinforcing effect of euphoria as well as that of drugs of abuse.25 Thus, one could postulate that the decrements in dopamine D2 receptors in obese individuals represent a downregulation to compensate for dopamine increases caused by chronic overstimulation from feeding. However, an alternative explanation is that individuals with low numbers of D2 receptors may be more vulnerable to addictive behaviours including compulsive food intake22. In this respect it is noteworthy that obese individuals with a binge-eating disorder are significantly more likely to have a family history of substance abuse than those in the general population.25 It has been postulated that compulsive disorders such as drug addiction, gambling, and obesity reflect a “reward deficiency syndrome”, that is thought to be due, in part, to a reduction in dopamine D2 receptors.27 This study provides direct evidence of a deficit in dopamine D2 receptors in obese individuals. We speculate that in obese individuals decrements in D2 receptors perpetuate pathological eating as a means to compensate for the decreased activation of reward circuits, which are modulated by dopamine.27 This study cannot discriminate if the brain changes in obese individuals are a consequence or a cause of the obesity. Further studies that assess D2 receptors measures before and after successful weight-reduction interventions might help determine if the low levels are due to changes secondary to the individual’s large BMI.

Although in this study we have focused on dopamine, it is important to point out that the regulation of body weight is complex and involves other physiological mechanisms and other neurotransmitters.2 In particular, the brain serotonergic and noradrenergic systems as well as the leptin OB receptor have been important targets in the development of drugs to treat obesity and these and other molecular targets merit investigation in obese individuals.1 The results from this study have implications for the treatment of obesity since they would suggest that strategies aimed at improving dopamine function might be beneficial in the treatment of obese individuals. In fact psychostimulant drugs (amphetamine,1 cocaine,1 and methylphenidate15), which increase extracellular dopamine, are anorexigenic14 and this effect is blocked by dopamine receptor antagonists.4 Unfortunately the therapeutic benefit of these drugs is curtailed by their addictive and psychoactive effects and to our knowledge there are currently no dopaminergic anorexigenic drugs that are not reinforcing. However, strategies to enhance dopaminergic function could involve behavioural interventions such as exercise. In animal models, exercise has been found to increase dopamine release14 and to raise D2 receptors.23 Further research to identify treatment approaches that enhance the function of the dopamine system as a means to promote long-term maintenance of weight control is warranted.
The fact that there were no differences in the K1 (delivery of [C-11]raclopride from plasma to brain) in striatum or in cerebellum between obese individuals and controls, and that there were no differences in striatal cerebellar metabolism, indicates that the differences in D2 receptor measures were not due to differences in bioavailability of the radiotracers between these two groups. The ability to find differences in regional brain glucose metabolism in obese individuals studied at baseline suggests that there are no major differences in regional brain activity during resting conditions in obese individuals when compared with controls. However, studies of regional brain glucose metabolism during stimulation by food or other rewarding stimuli may show abnormalities in regional brain activity in obese individuals.

Although we are interpreting the reduction in Bmax/kd in the obese individuals as evidence of a reduction in dopamine D2 receptors, methodologically we cannot rule out the possibility that the results are due to increase in the concentration of extracellular dopamine, since [11C]raclopride competes with dopamine for binding to the dopamine D2 receptors. However, this is unlikely since the pharmacological evidence indicates that enhanced dopamine activity is associated with reduced food intake.

**Contributors**

Gene-Jack Wang was the main clinical coordinator, did the PET scanning, and wrote the paper. Nora Volkow designed the study, analysed PET data, and wrote the paper. Jean Logan and Christopher Wong analysed the PET scan data and were responsible for data management. Naomi Pappas was responsible for study coordination and recruitment of participants. Noel Netusil participated in PET scanning. Wei Zhu did the statistical analysis and wrote the paper. Joanna Fowler was the principal investigator of the study, responsible for radiochemistry, and wrote the paper.

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**References**